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Brett M. Hutton, Esq.
Heslin Rothenberg Farley & Mesiti P.C.
5 Columbia Circle
Albany, NY 12203

EXAMINER
FORD, JOHN K

ART UNIT	PAPER NUMBER
3743	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/056,237	Wisniewski et al.
	Examiner	Art Unit
	FORD	3743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10-15-02.

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) 1-42 is/are pending in the application.

4a) Of the above claim(s) 9-26 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) 1-8 and 27-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☑ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☑ Information Disclosure Statement(s) (PTO-1449) ~~Paper No~~(s) 2/25/03

18)☐ Interview Summary (PTO-413) Paper No(s). _____ .

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

Applicant's response of October 15, 2002 (Paper No. 3) has been studied carefully. Applicant's election of method claims 1-8 and 27-42 and the first species (of Figure 1 and 2) is acknowledged. Of the elected method claims counsel states all of these are readable on the species elected. The examiner disagrees with counsel's assessment of all of the elected claims being generic to a host of there species, but a detailed analysis will wait until an independent claim is allowed.

Applicant's traverse of the restriction and election requirements is unpersuasive. These cases and their parents are already a significant burden. Spending significant time searching out the minutia of each of a large number of alternative species is a poor use of limited examination time. Regarding the method/apparatus restriction the Examiner stands by his statements made in Paper No. 2, particularly the case law cited on page 3 penultimate paragraph. For his part, applicant has not commented on any of these cases. The traverse is unpersuasive. The election and restriction requirements are both made final.

Prior Art Necessary for Proper Examination

The examiner needs an exact publication date (month and day) for each of the 1996 articles (Advanstar and the Drug Manufacturing Technology Series, Vo. 2) to ascertain their prior art status as to this application. It is noted that both 1996 publications have authorships that differ from the current inventive entity and hence would be prior art under 102(a) and the case law interpreting "another". If counsel insists the 1996 publications are not prior art, please address in detail his reasons why they are not. Please address some comments to the differing inventive entity vis-à-vis

the authorship entity, and why they should not be treated as disparate under 35 USC 102(a).

On pages 2 and 3 of the specification under a section entity "Description of the Prior Art" applicants appear to disclose that liquids, possibly biopharmaceuticals, have been heated and cooled in containers which have structures comprising "extensions of the container or any structures in the container". Fins are mentioned specifically but are "typically attached to the container or an internal structure at only one point".

Full disclosure of this prior art is needed. If applicant does not have a publication, a carefully drawn sketch with meaningful legends and explanations is required. Disclosure of what processes (e.g. heating, cooling, freezing etc.) have been performed in this acknowledged prior art described on pages 2 and 3 of the specification is required as well as what fluids (e.g. biopharmaceuticals etc) have been processed in the acknowledged prior art container.

Moreover the 1992 disclosure of Wisniewski and Wu does not disclose how close to the wall of the container the heat transfer fins extended, the dimensions of those fins (length, width, height and thickness), the diameter of the container and the volume of the container. Because applicants are reasonably deemed in possession of this information or could ascertain it quickly by looking through their records and or contacting Genentech directly so that measurements could be made (given the fact that they built it while at least one of the inventors was at Genentech) and the examiner has no other reasonable way to obtain it, a requirement under Rule 1.56 is set forth here. Timely submission of this information will permit an orderly examination and will avoid

the Board having to require such information under Rule 1.196(d) should an appeal be forthcoming.

Applicants assert, without further discussion, in SN 09/443,838, Paper No. 9 that the information that the Examiner is now requesting is "cumulative" to information already on file. The information the examiner has required in the three paragraphs above is not found in any of the prior art submitted by Applicant thus far. If Applicants do not agree, please point out specifically in the prior art submitted where the Examiner can find prior art disclosure corresponding to that discussed the three previous paragraphs. If applicants cannot do that, then provide the information the Examiner has requested above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 27-42 are rejected under 35 U.S.C. 112, second paragraph.

The term "biopharmaceutical product" as it is used in this application is ambiguous and hence its use in claims 1, 27 and 35 is also the source of ambiguity. In contrast with what may be accepted "biopharmaceutical products" such as a product derived from biological sources that has an intended therapeutic application and whose manufacturing is or will be regulated by pharmaceutical or veterinary regulator agencies (see '132 declarations in Paper No. 4 of SN 09/443,838), in the specification applicants state that the present invention can be used "freeze and preserve a variety of biopharmaceutical products, including but not limited to proteins, cells, antibodies,

medicines, plasma, blood, buffer solutions, viruses, serum, cell fragments, cellular components, and any other biopharmaceutical product."

Many of the purported biopharmaceuticals on applicants' list in the specification are not normally considered biopharmaceutical products by applicants' definition (offered up in the '132 declarations in Paper No. 4 of SN 09/443,838) above. For example, buffer solutions are acids or bases-dissolved in water not derived from biological sources nor regulated by FDA to the Examiner's knowledge. Blood, per se, such as is drawn from the general population by the Red Cross would not appear to be a biopharmaceutical by affiants' definition yet it appears on applicants' list. On page 133, col. 1, fourth full paragraph, of the 1992 Wisniewski and Wu prior art, it states that "buffer salts" can be components of a biopharmaceutical product but it appears the "buffer salts" are not themselves a biopharmaceutical product. "Medicines" (also on applicant's list disclosed in the specification) are simply understood to be drugs or other agents used to treat disease or injury. They need not be derived from biological sources. What is vital to this examination is to know, with reasonable particularity, what chemicals, when placed in applicants' tank, would infringe the claims. Under applicant's expansive definition of biopharmaceuticals in the specification, it would appear that many conventional organic and inorganic solutions (e.g. buffer solutions) would be included – against what affiants Arathoon, Burman, Lawlis and Vetterlein (Paper No. 4 of SN 09/443,838) would consider to be the reasonable limits of the word. On the other hand, orange juice recently shown to have a measurable effect against certain forms of cancer, was suggested by counsel to not seriously be considered a biopharmaceutical,

in the prosecution of the parent applications. The Examiner disagrees. If buffer solutions are considered to be biopharmaceuticals and blood, per se, drawn from the general population is biopharmaceutical, it doesn't seem reasonable to exclude orange juice. The chances of the FDA regulating "buffer solutions" as a pharmaceutical in the future would be about on par with the chances of the FDA regulating orange juice as a biopharmaceutical in the Examiner's opinion. If the definition now includes orange juice based on new research showing its anticancer properties and possible further regulation by the FDA, then applicants' use of the word biopharmaceutical seems to include an ever growing and somewhat amorphous list of chemicals that would be perpetually changing as new research was done to show therapeutic properties to products produced by biological processes such as photosynthesis, fermentation and biological agents such as herbs, roots and compounds which are essentially the products of nature. It is impossible to know which of these will be regulated by the FDA in the future given the vicissitudes of government regulation. The term as it is used in the application is deemed by the Examiner to be one that violates the tenets of 35 U.S.C. 112, second paragraph, in that the metes and bounds of the claims cannot be established with the requisite clarity required by the statute and are subject to change based on *future* FDA actions. The would-be infringer would have no clear way of determining infringing behavior, to put it another way. Infringement would be constantly changing depending on what the FDA decided to regulate as a biopharmaceutical. It is noted that the FDA regulates the handling and composition many food items, but that doesn't transform them into biopharmaceuticals even if those food items have some therapeutic benefit.

The definition offer by the declarants appears to be unworkable in the Examiner's opinion and that offered in the specification ambiguous.

The declarations under Rule '132 by Arathoon, Burman, Lawlis and Vetterlein (see Paper No. 4 of SN 09/443,838) all appear to define "biopharmaceutical products" much more narrowly than the expansive definition given in the specification and in the 1992 article by Wisniewski and Wu. For example, the Examiner knows of no biologically sources "buffer solution" which in and of itself is regulated by the FDA. Moreover, if there were such a solution, why would it freeze any differently than a buffer solution not regulated by the FDA no biologically sources? It is noted that there is a tremendous variety of "biopharmaceutical products" in applicants' list some of which are very large: cells (e.g. blood etc.) whereas others are millions if not billions of items smaller (e.g. viruses or salt ions in a buffer solution). It is submitted that the freezing characteristics of solutions at these two extremes would be extremely different. Blood would probably freeze more in the manner of orange juice or milk given its nearly macroscopic cellular nature whereas virus in a suitable buffer solution of water would freeze in the manner of pure or salty water. Moreover, Applicants' response in a pre-final amendment in SN 09/443,838 as well as the declarations under Rule '132 have failed to reconcile the definition of "biopharmaceutical products" stated in the declarations with the disclosure of the chemicals and blood products, medicines, buffers etc. offered up as examples of "biopharmaceutical products" in the specification. The specification definition of biopharmaceutical products clearly encompasses more chemicals than Affiants' declaration under Rule '132. To the extent that the Rule '132

declarations define the term "biopharmaceutical product" more narrowly that what is discussed in the specification, the declarations serve to heighten the ambiguity of the disclosed and claimed "biopharmaceutical products" and what the limits (metes and bounds) of that terminology is to have as a claim limitation. Moreover, in regard to the cited prior art, nothing in the declarations has addressed why one designing freezing equipment for the chemicals disclosed in the specification would not look to the art of freezing water, orange juice or solids suspended in liquids.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 27-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of the 1992 publication by Wisniewski and Wu and the 1986 Kalhori and Ramadhyani article entitle "Studies on heat transfer from a vertical cylinder with or without fins, embedded in a solid phase change medium" (reference 29 on page 140 of the 1992 article by Wisniewski and Wu) and West USP 2,114,642.

The 1992 Wisniewski and Wu research paper appears to disclose every feature of the claimed invention including heat exchange member (i.e. fins) in close spaced proximity to the interior surface of the container. It lacks a "spur tube" type cooler in the center. See Figure 1 and the description thereof found on pages 134 and 136. Note

page 135 should follow page 136 and was apparently printed out of order. The Examiner did not catch this error when he examined SN 08/895,782.

There is not explicit disclosure of any thermal ice bridge in the 1992 Wisniewski and Wu research paper (if that what is being claimed in the phrase "thermal transfer bridge", however see specification, page 5, lines 10-13, for apparently inconsistent definition: when the medium is being heated, after being frozen, the ice in the "gap" claimed between the tips of the fins and the wall of the container melts quickest leaving liquid in the "gap", hence it would appear that "thermal transfer bridge" is much broader term than simply an ice bridge) formed between the tips of these fins and the interior wall of the container and no explicit disclosure of how close to the container wall these heat transfer fins extend, although they must extend far enough to define "compartments" between the fins (1992 Wisniewski and WU research paper, page 136, first full paragraph).

The thermal bridge of ice will inherently form between the tip of the heat transfer fins and the interior of the container because they are the closest points to one another and both are actively cooled by circulating cooled silicon oil. Closely spaced cooled surfaces are known by those of skill in the refrigeration art to form ice bridges when a liquid is being frozen into a solid.

As evidence to support the Examiner's statement that the closely spaced cooled surfaces will inherently form ice bridges (see MPEP 2112-2112.02, dealing with inherency, incorporated here by reference), the reader is referred to Voorhees USP

983,466, page 1, col. 2, line 97 – page 2, col. 1, line 5 (Voorhees is not relied upon explicitly here, see MPEP 2131.01, sub-section III), wherein it states:

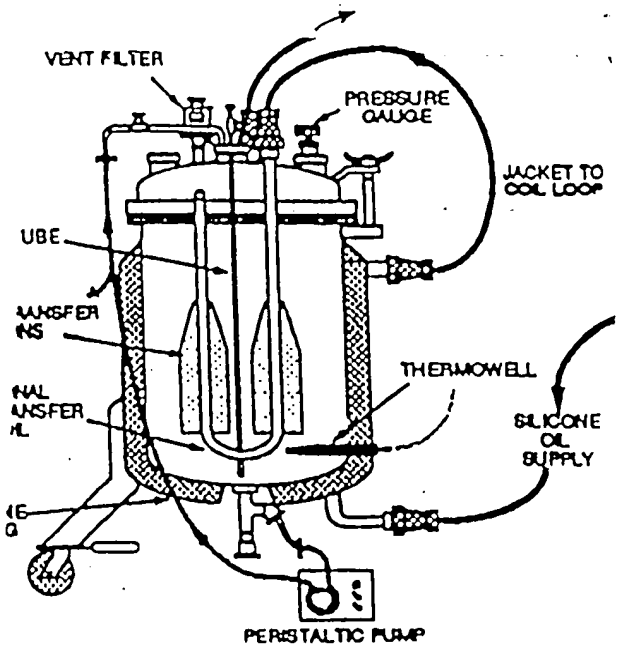
"Whether ice forms in single cakes about several freezing elements or forms in a single cake enclosing a plurality of such elements depends upon the spacing of the several freezing elements from each other. In the first instance of course, ice forms separately about each freezing element, but if these elements be ***close together*** the ice surrounding these element will ***coalesce into a single cake***; and after this has occurred freezing will go on from the surface of the combination cake so formed." (Emphasis supplied).

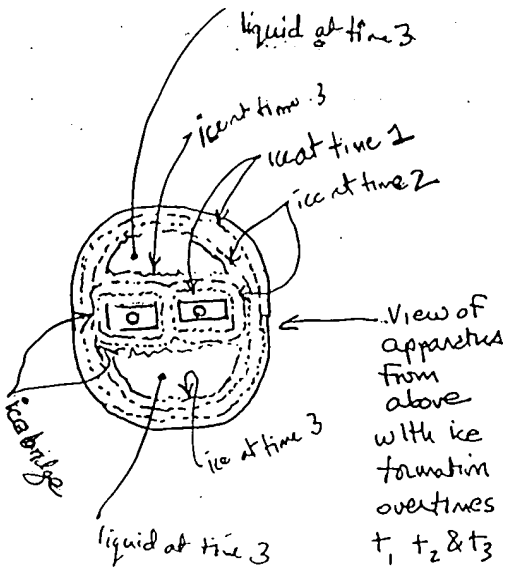
Furthermore, Voorhees, page 2, col. 1, lines 14-21 states:

"I have shown a number of other elements so spaced relatively as to form a single cake 15 of length comparable to cakes formed in plate processes. Of course if the ***freez-ing were continued indefinitely the cakes 12, 13, 14 and 15 would eventually coalesce and freeze to the sides of the tank...***"

It is evident that ice will build upon the heat exchanger and walls of the vessel shown in Figure 1 of 1992 Wisniewski and Wu research paper, during the freezing phase, until they bridge as shown in the diagrams below, a fact that can be established by basic scientific principles. Burroughs et al. USP 3, 318,105 illustrates the phenomena. As is clearly seen in Figs. 1A-1C ice builds up evenly cooled surfaces and even as the top surface freezes the ice coating on the submerged surfaces continues to build up more or less evenly. The same type of analysis is disclosed by Finnegan USP 2,129,572, illustrating that the time required to freeze a substance varies "approximately

as the square of the thickness of such substance" with slower freezing generally leading to undesirable concentration effects (what applicants and the 1992 Wisniewski and Wu research paper refer to as "cryoconcentration"). Finnegan, like the 1992 Wisniewski and Wu research paper, discloses the use of heat exchange fins (projecting inwardly from the exterior wall of the container in the case of Finnegan) to form compartments within the tank to speed the freezing process. Finnegan illustrates using a series of dotted lines how the freezing process progresses over time in various geometries of heat exchange fins. Applying this same science (illustrated by Burroughs and Finnegan) to the system disclosed by 1992 Wisniewski and Wu research paper yield the results illustrated on the next page for the system disclosed by the 1992 Wisniewski and Wu research paper in Figure 1.





Even if the 1992 Wisniewski and Wu research paper is deemed not to disclose heat exchanger fins "in close spaced proximity" to the container wall, to have extended the fins in Figure 1 of the 1992 Wisniewski and Wu publication to a point "in close spaced proximity" to the interior surface to the container in order to advantageously increase the rate of heat transfer and "divide the tank volume into compartments to decrease the freezing the thawing time and to reduce cryoconcentration effects" (1992 publication, page 136, col. 1, first full paragraph) would have been obvious to one of ordinary skill in the art.

The examiner submits that the fins shown in Figure 1 of the 1992 Wisniewski and Wu publication are already in spaced proximity to the interior wall of the container such that substantially discrete compartments are formed (see page 136, col. 1, first full paragraph), an effect that would be enhanced if the fins were further extended to a point closer to the interior wall of the container.

Moreover, larger fins would increase the amount of surface area for heat transfer, giving an added advantage. On page 136 of the 1992 Wisniewski and Wu publication it states that the "fin's length, thickness and shape were designed to maintain ***efficient heat transfer*** during freezing and thawing." (Emphasis supplied). It is not open to any serious debate that larger, thicker, fins that extend to points closer to the interior wall of the container are more efficient heat transfer vehicles than smaller, thinner fins that do not extend to points closer to the interior wall of the container.

The 1992 Wisniewski and Wu publication states on page 136: "The heat transfer fins were configured to ***divide the tank into compartments*** to decrease the freezing and thawing time and to reduce cryoconcentration effects. ***Compartmentation*** of the tank is especially effective for maintaining liquid in a static state to minimize cryoconcentration." (Emphasis supplied). The fins are designed to maintain "efficient heat transfer during freezing and thawing" (page 134, col. 2, 1992 Wisniewski and Wu publication). Figure 1, (page 134) of the 1992 Wisniewski and Wu publication clearly shows heat transfer fins extending outwardly for the internal heat transfer coil towards the interior wall of the container. Extending the fins further outwardly to aid in the formation of compartments to minimize cryoconcentration would have been another motivation to one of ordinary skill in the art to make the same modification.

West (USP 2,114,642) teaches, in Figures 3, 5 and 6, a central spur-tube heat exchanger used in combination with an external cooler (shown in Figure 6) to cool and freeze product as shown in Figure 5. Such a cooler advantageously reduces cryo-concentration as discussed on page 2, col. 1, line 73 – page 2, col. 2, line 33, incorporated here by reference. As shown in Figure 5, the fins 15 extend radially outward to a point close to the container 8 and thereby "compartment" the to be frozen substances.

The 1986 Kalhori and Ramadhyani article entitled "Studies on heat transfer from a vertical cylinder, with or without fins, embedded in solid phase change medium" (reference 29, on page 140 of the 1992 article by Wisniewski and Wu), like applicants have disclosed in Figures 1 & 2 of their drawings, shows, in Figure 3, a "spur-tube" type

heat exchanger with six heat transfer fins welded to it in a manner almost identical to what applicants show in Figures 1 and 2 of the current application. The finned heat exchanger, as shown, is immersed in a container of paraffin and the melting and freezing processes were studied in great detail using a material, paraffin, of known characteristics. See the abstract of this article, on the first page. Again, fins that span nearly the entire interior of the container were found to be especially effective, with a host of definitive technical data presented (that is unnecessary to discuss here) showing the virtues of these large fins in improving heat exchange. See last sentence of article- "In view of the ***superior heat transfer characteristics, the finned cylinder*** is a much better choice of the design of a practical thermal storage unit." (Emphasis supplied).

In view of each of the above teachings, it would have been obvious to one of ordinary skill in the art to have extended the fins of the prior art disclosed in the 1992 article by Wisniewski and Wu to substantially the inner periphery of the container, leaving a small gap to permit the heat exchanger to be removed for cleaning (as is disclosed to be necessary in the 1992 article by Wisniewski and Wu page 136). Extending the fins to substantially the inner periphery of the container would, advantageously, have the following effects:

a. Improve heat transfer by increasing heat transfer surface area,

b. Improve "comparmentation" by forming ice bridges and

c. Reduce cryoconcentration.

To have replaced the centrally mounted tubular heat exchanger and fins of the 1992 article by Wisniewski and Wu disclosed in Figure 1 with the spur-tube heat

exchanger and fins shown by Kalhori and Ramadhyani in Figure 3 or that shown by West (at 15, in Figure 5) for the purpose of improving heat transfer and to facilitate ease of construction as well as to facilitate easy removal from the frozen mass would have been obvious to one of ordinary skill in the art.

Any inquiry concerning this communication should be directed to John Ford at telephone number 703-308-2636.

John Ford
Primary Examiner
Art Unit 3743

John K. Ford
Primary Examiner